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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,681	01/16/2002	Daniel Cohen	G-101.US05REG	1458

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,681	COHEN ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-43* is/are pending in the application.

4a) Of the above claim(s) *19,22-29 and 33-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/02, 1/03, 11/03, 3/1/04, 3/29/04, 9/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-18 been canceled. Claims 19-43 are at issue and are present for examination.

Applicant's election with traverse of Group II, claims 20-21 and 30-32 and SEQ ID NO:7 in the response filed 11/8/04 is acknowledged. The traversal is on the ground(s) that there would not be an undue burden of search for the coexamination of the species of SEQ ID NOS: 7-10. This is not found persuasive because each of these splice variants of the DAO gene is a patentably distinct protein having different structural characteristics and potentially distinct functional characteristics such that each variant may have a distinctly different relationship to the disorders disclosed in the specification and claims. As such each variant would require an independent search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 19, 22-29, and 33-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/8/04.

The information disclosure statement filed 12/30/02 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy

of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The information referred to therein has not been considered except for the US Patents cited therein for which copies are not required and those non-patent literature references specifically initialed on applicants 1449 which were cited by the examiner herein. It is noted that the letter accompanying this IDS indicates states that copies were provided but no copies of these references are present in the application. If applicants wish the remaining references to be considered, copies must be provided. Applicant should further note that the citations listed as R85-R97 of this IDS are identical to the citations listed as R85-R97 on IDS submitted 1/22/03 copies of which are present in the case and thus do not need to be submitted.

Claims 20 and 21 are objected to because of the following informalities: abbreviations (i.e., DAO and DDO) should not be used in the claims without reciting the full terminology for which they are used unless they are common within the art. Appropriate correction is required.

Claims 20, 21 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 (upon which claims 30-32 depend) is indefinite in the recitation of "DAO or DDO polypeptide or a biologically active fragment thereof" as the specification does not define what "biological activities" are present with DAO and/or DDO polypeptides and thus the scope of fragments encompassed by the instant recitation is unclear. Is this activity limited to DAO or DDO enzymatic activity or does it encompass other activities as well. If so what other activities?

Claim 21 (upon which claims 30-32 depend) is unclear because step (a) recites the use of either a DAO or DDO polypeptide and step (c) recites comparing the DAO or DDO activity of the polypeptide, with and with the test compound while step (b) recites only detecting the level of DAO activity. As such it is unclear if Claim 20 includes monitoring DDO activity or not. If the testing of DDO activity is included step (b) should be amended to recite detecting the level of DAO or DDO activity.

Claims 20 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of use of a genus of D-amino acid oxidase (DAO) or D-aspartate oxidase (DDO) polypeptides. The specification teaches the structure of only a few representative species of such DAO and DDO polypeptides. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having DAO or DDO activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 20 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying a candidate molecule for the treatment of schizophrenia, depression, or bipolar disorder comprising determining whether a compound reduces enzymatic activity of the DAO of SEQ ID NO:7, does not reasonably provide enablement for methods of identifying a candidate molecule for the treatment of

schizophrenia, depression, or bipolar disorder comprising determining whether a compound reduces any DAO or DDO biological activity nor methods of identifying a candidate molecule for the treatment of schizophrenia, depression, or bipolar disorder comprising determining whether a compound reduces DDO enzymatic activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants claims recite methods for identifying a candidate molecule for the treatment of schizophrenia, depression, or bipolar disorder comprising determining whether a compound reduces any DAO or DDO biological activity or binding activity. The specification establishes that a candidate schizophrenia-related gene product (g34872) binds to human D-amino acid oxidase (SEQ ID NO:7) in a yeast two-hybrid screen (paragraph 18) and the g34872 polypeptide acts as an activator of DAO enzymatic activity on a dose-dependent basis (see examples 1-5). Furthermore, the prior art teaches that mammalian DAO is the endogenous degradative enzyme for the neurotransmitter D-serine (see Snyder et al., Reference R47 of applicants IDS of 12/30/02) the levels of which have been clearly linked to schizophrenia and depression (see Tsai et al.,

US-PGPUBS 2002/0035145, Tsai et al., 1998 or Heresco-Levy, Reference R4 of applicants IDS of 11/17/03). As such the link between mammalian DAO enzymatic activity and schizophrenia, depression, or bipolar disorder seems reasonable. However, there is no evidence in the specification to link other "biological activities" of DAO such as immunological or binding activities with schizophrenia, depression, or bipolar disorder and without a clear indication of what activities are present in mammalian DAOs and how these activities relate to the instant disorders one of skill in the art would not be able to identify candidate compounds for the treatment of these disorders by determining if a compound inhibits any activity of any DAO. Furthermore, the scope of DAO enzymes recited in the claimed methods is clearly not commensurate in scope with the enabled invention. Claims 20 and 30-32 recite the use of any DAO polypeptide. While the art teaches a large number of naturally occurring DAO proteins, DAOs produced by organisms other that mammals differ substantially in structure from the human DAO of SEQ ID NO:7. In view of the large structural differences between known DAO proteins, one of skill in the art would not reasonably expect that any DAO could be used in the claimed methods as inhibitors of structurally dissimilar DAOs would be unlikely to inhibit the mammalian DAOs and therefore would be

unlikely to be useful for the treatment of schizophrenia, depression or bipolar disorder. Furthermore, while the specification and art provide a clear link between DAO enzymatic activity and schizophrenia, depression, or bipolar disorder, the specification fails to provide any evidence to support a link between any DDO activity including enzymatic activity and these disorders. While DAO and DDO have related enzymatic activities, their substrates are mutually exclusive. DDO does not act on D-serine nor any other substrate of DAO and DAO does not act on the known DDO substrates (i.e., D-aspartate and D-glutamate). While D-aspartate is a naturally occurring substrate of DDO which may have a neuroendrocrine role, its physiological role is not known and appears to be distinct from that of D-serine (see Wolosker et al. and Schell et al., Reference R44 of applicants IDS of 12/30/02). As such one of skill in the art would not expect to be able to identify candidate compounds for the treatment of schizophrenia, depression, or bipolar disorder by determining if a compound inhibits any activity of DDO.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the

> art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast et al. (US PG-PUBS 2004/0053989) in view of Swiss-Prot Accession No. P14920.

Prendergast et al. teach that inhibitors of the enzyme D-amino acid oxidase are useful for the treatment of neurodegenerative diseases such as Alzheimer's disease (see paragraph 212). Prendergast do not teach an assay for DAO inhibitors.

Swiss-Prot Accession No. P14920 teaches the human DAO enzyme which enzyme is indentical to SEQ ID NO:7 of the instant application.

As Prendergast et al. teach that DAO inhibitors have use in the treatment of Alzheimers and other diseases it would have been obvious to one of skill in the art to test compounds for their ability to inhibit the enzymatic activity of the human DAO

of Swiss-Prot Accession No. P14920 by comparing the activity of the enzyme in the presence and absence of the compound.

Claims 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast et al. (US PG-PUBS 2004/0053989) in view of Swiss-Prot Accession No. P14920 as applied to claim 21 above, and further in view of Ricci et al. (Reference R43 of applicants IDS of 12/30/02).

Prendergast et al. and Swiss-Prot Accession No. P14920 are discussed above and make obvious the screening of compounds for human DAO inhibitory activity.

Ricci et al. teach that aminoethylcysteine-ketimine and derivatives thereof strongly inhibit hog kidney DAO. It is well known in the art that mammalian DAO enzymes are highly homologous both structurally and functionally. As such one of ordinary skill in the art would expect that inhibitors of the hog-kidney enzyme would inhibit the human enzyme and be useful for treating humans. Furthermore, it is well known to organic chemists to that derivatives of a compound with a desirable functional activity are likely to have similar activity. Therefore, it would have been obvious to one of skill in the art to use the aminoethylcysteine-ketimine and derivatives thereof of Ricci et al. as the test compound in the assays made obvious

by the combined disclosures of Prendergast et al. and Swiss-Prot Accession No. P14920..

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai et al (US PG-PUBS 2002/0035145) in view of Wake et al. and Swiss-Prot Accession No. P14920.

Tsai et al. teach that agonists of the glycine site of the NDMA receptor can be used for the treatment of schizophrenia and depression (see paragraph 5).

Wake et al. teach that D-serine is the endogenous agonist of the glycine site of the NDMA receptor, that the enzyme D-amino acid oxidase degrades D-serine and that therefore DAO may exert modulatory action on NDMA receptor activity by controlling the concentration of D-serine (see page 25). Wake et al. further show that mice lacking in DAO activity which have elevated levels of endogenous D-serine also have exaggerated responses to known NDMA receptor stimuli, i.e., the mice exhibit enhanced NDMA receptor mediated synaptic transmission. Wake et al. also teach that exogenously applied inhibitors of DAO enhance NDMA currents (see paragraph spanning pages 27 and 28).

Swiss-Prot Accession No. P14920 teaches the human DAO enzyme which enzyme is identical to SEQ ID NO:7 of the instant application.

As Wake et al. teach that DAO inhibitors enhance NDMA currents and Tsai et al. teach that agonists of NDMA receptors are useful for the treatment of schizophrenia and depression, one of skill in the art would reasonably expect inhibitors of DAO to be useful for the treatment of schizophrenia and depression. Therefore, it would have been obvious to one of skill in the art to test compounds for their ability to inhibit the enzymatic activity of the human DAO of Swiss-Prot Accession No. P14920 by comparing the activity of the enzyme in the presence and absence of the compound with the expectation that compounds which inhibit DAO would be useful for the treatment of schizophrenia and depression.

Claims 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai et al (US PG-PUBS 2002/0035145) in view of Wake et al. and Swiss-Prot Accession No. P14920 as applied to claim 20 and 21 above, and further in view of Ricci et al. (Reference R43 of applicants IDS of 12/30/02).

Tsai et al (US PG-PUBS 2002/0035145), Wake et al. and Swiss-Prot Accession No. P14920 are discussed above and make obvious the screening of compounds for human DAO inhibitory activity.

Ricci et al. teach that aminoethylcysteine-ketimine and derivatives thereof strongly inhibit hog kidney DAO. It is well

known in the art that mammalian DAO enzymes are highly homologous both structurally and functionally. As such one of ordinary skill in the art would expect that inhibitors of the hog-kidney enzyme would inhibit the human enzyme and be useful for treating humans. Furthermore, it is well known to organic chemists to that derivatives of a compound with a desirable functional activity are likely to have similar activity. Therefore, it would have been obvious to one of skill in the art to use the aminoethylcysteine-ketimine and derivatives thereof of Ricci et al. as the test compound in the assays made obvious by the combined disclosures of Tsai et al (US PG-PUBS 2002/0035145), Wake et al., and Swiss-Prot Accession No. P14920.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai et al (US PG-PUBS 2002/0035145) in view of Snyder et al. (Reference R47 of applicants IDS of 12/30/02), and Swiss-Prot Accession No. P14920.

Tsai et al. teach that agonists of the glycine site of the NDMA receptor, particularly D-serine, can be used for the treatment of schizophrenia and depression (see paragraph 5).

Synder et al. teach that D-serine is the endogenous agonist of the glycine site of the NDMA receptor, that the enzyme D-amino acid oxidase is the endogenous enzyme which degrades D-serine and mice lacking DAO possess elevated levels of D-serine

(see page 554). Synder et al. further show that exogenously applied DAO inhibits NDMA neurotransmission (see page 557) and that this inhibition can be fully reversed by D-serine application.

Swiss-Prot Accession No. P14920 teaches the human DAO enzyme which enzyme is identical to SEQ ID NO:7 of the instant application.

As Synder et al. teach that mice lacking DAO possess elevated levels of D-serine and that regions of normal brains exhibiting high levels of DAO activity exhibit low levels of D-serine and vice versa, one of skill in the art would reasonably expect that inhibiting DAO activity in normal brains would result in increased levels of D-serine. As Tsai et al. teach that agonists of NDMA receptors, and in particular D-serine are useful for the treatment of schizophrenia and depression, one of skill in the art would reasonably expect inhibitors of DAO to be useful for the treatment of schizophrenia and depression. Therefore, it would have been obvious to one of skill in the art to test compounds for their ability to inhibit the enzymatic activity of the human DAO of Swiss-Prot Accession No. P14920 by comparing the activity of the enzyme in the presence and absence of the compound with the expectation that compounds which

inhibit DAO would be useful for the treatment of schizophrenia and depression.

Claims 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai et al (US PG-PUBS 2002/0035145) in view of Synder et al. (Reference R47 of applicants IDS of 12/30/02) and Swiss-Prot Accession No. P14920 as applied to claim 20 and 21 above, and further in view of Ricci et al. (Reference R43 of applicants IDS of 12/30/02).

Tsai et al (US PG-PUBS 2002/0035145), Synder et al. and Swiss-Prot Accession No. P14920 are discussed above and make obvious the screening of compounds for human DAO inhibitory activity.

Ricci et al. teach that aminoethylcysteine-ketimine and derivatives thereof strongly inhibit hog kidney DAO. It is well known in the art that mammalian DAO enzymes are highly homologous both structurally and functionally. As such one of ordinary skill in the art would expect that inhibitors of the hog-kidney enzyme would inhibit the human enzyme and be useful for treating humans. Furthermore, it is well known to organic chemists to that derivatives of a compound with a desirable functional activity are likely to have similar activity. Therefore, it would have been obvious to one of skill in the art to use the aminoethylcysteine-ketimine and derivatives thereof

of Ricci et al. as the test compound in the assays made obvious by the combined disclosures of Tsai et al (US PG-PUBS 2002/0035145), Synder et al., and Swiss-Prot Accession No. P14920.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652